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K2P channels and their protein partners

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A decade since their discovery, the K2P channels are recognized as pathways dedicated to regulated background leakage of potassium ions that serve to control neuronal excitability. The recent identification of protein partners that directly interact with K2P channels (SUMO, 14-3-3 and Vpu1) has exposed new regulatory pathways. Reversible linkage to SUMO silences K2P1 plasma membrane channels; phosphorylation of K2P3 enables 14-3-3 binding to affect forward trafficking, whereas it decreases open probability of K2P2; and, Vpu1, an HIV encoded partner, mediates assembly-dependent degradation of K2P3. An operational strategy has emerged: tonic inhibition of K2P channels allows baseline neuronal activity until enhanced potassium leak is required to suppress excitability.

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Introduction

Potassium leak through K2P channels: a trickle becomes a flood

Potassium leak pathways that are active at rest stabilize membrane potential below the firing threshold of excitable cells. Although the existence of leak currents was proposed in 1952 by Hodgkin and Huxley [1,2], they remained a biophysical curiosity for more than 4 decades [3,4]. Identification of the first molecular correlate of a potassium leak current was preceded by the cloning of novel potassium channels from *Saccharomyces cerevisiae* and *Caenorhabditis elegans* with two pore-forming P loops in each subunit [5] (Figure 1a). Thereafter, K2PØ (dORK; see glossary) was cloned by functional expression from the neuromuscular tissue of *Drosophila melanogaster* [3]; biophysical characterization revealed K2PØ to be a potassium selective channel with the predicted attributes of a background leak conductance, that is, a voltage independent portal that shows Goldman-Hodgkin-Katz (open) rectification (see glossary) [3,6,7]. When the concentration of potassium is symmetrical across the membrane, K2PØ currents change in a linear manner as a function of voltage. Under physiological conditions (high internal and low external potassium), K2PØ behaves like an open rectifier passing greater outward than inward currents (Figure 1b).

A striking feature of K2PØ is the body plan of its subunits: each has 2 P loops and 4 transmembrane domains (TM) (Figure 1a). The distinct 2P–4TM topology is predicted for more than 70 homologs of K2PØ present in genome databases. Fifteen mammalian genes encode K2P channels and are designated as the *KCNK* genes (Figure 1c) [8]. K2P channels are expressed throughout the body; their distribution in the central nervous system (CNS) has been particularly well-delineated [9]. Classical voltage-gated and inward rectifier potassium channel subunits have only one P loop and assemble in groups of four to create a central permeation pathway [10,11]. It is of little surprise then that pairs of K2P subunits come together to form functional pores [12], and to manifest permeation characteristics [7] and some pore-dependent gating behaviors similar to those of their classical tetrameric forebears [6].

As expected for regulators of excitability, K2P channels are under tight control from a plethora of chemical and physical stimuli including oxygen tension, pH, lipids, mechanical stretch, neurotransmitters and G-protein coupled receptors; the channels are also the molecular targets for certain volatile and local anesthetics (c.f., [8,13]). Regulation of K2P channels alters those attributes that are subject to change in any ion channel: number of pores at the site of operation, open probability and unitary current [4].

The discovery of the K2P family of channels has elevated leak from an electrophysiological nuance to an acknowledged, dynamic determinant of cellular excitability. Although the study of these proteins is still in its infancy, the gap in understanding between K2P channels and their well-established relatives is closing. One area of progress is the delineation of interactions with other proteins. Here, we focus on three K2P partners, the identification of which sheds light on unappreciated control mechanisms that might prove to be general because they appear to operate on other proteins.

Peptide modification at the plasma membrane is (un)exciting

K2P1 (also known as TWIK1, KCNK1 and hOHO) was the first reported example of a mammalian K2P channel

Glossary

Dibasic retention motifs and coatamer proteins: Basic amino acid residues (R, K) that are often in pairs (but seen singly or in triplets) that serve as recognition motifs for coatamer proteins. Vesicles coated with coat protein complexes, coatomer proteins, such as β-COP, mediate retrograde transport to the endoplasmic reticulum.

Goldman-Hodgkin-Katz (GHK) rectification and open rectification: The current–voltage relationship observed when ions go through an open, ion-selective portal. K2PØ has a linear current–voltage relationship when potassium ions are the same on both sides of the membrane but only significant outward currents are seen under physiological conditions of high internal and low external potassium. Underlying electrodiffusion assumptions are inaccurate yet GHK theory predicts some observed nonlinear relationships quite well.

K2PX channel gene and protein names [8]: K2PØ was the first functional K2P channel; cloned from *d. melanogaster* it is an open (or GHK) rectifier and given the gene name dORK. The mammalian proteins are formally named thereafter K2P1, K2P2, etc., and the encoding genes names accordingly, *KCNK1*, *KCNK2*, etc., Figure 1 indicates names in common usage for the proteins.

TALK: K2P16 and K2P17 show more activity when bath solution is alkaline.

TASK: K2P3 and K2P9 are acid-sensitive channels inhibited by protonation of a histidine in the first P domain with lowered bath pH.

TREK: K2P2 so-called in early reports for TWIK-related.

TWIK: At first thought to be a weak inward rectifier, K2P1 is recognized to be a classical open rectifier once activated by desumoylation [19•].

[14–16] and is widely expressed with abundance in cerebellum, thalamus [9], heart [17] and kidney [18]. Functional study of the channel has been perplexing. In contrast to early reports indicating that cloned K2P1 produced inwardly rectifying potassium currents in *Xenopus laevis* oocytes, hence the alias TWIK [14], concurrent investigations were unable to recapitulate functional expression [15,16]. These frustrations hampered efforts to delineate the biophysical attributes of the channel or to correlate the clone with native currents.

Recently, K2P1 subunits were shown to manifest robust, polarized expression at the surface of *Xenopus laevis* oocytes [19••]. We speculated that K2P1 might need to assemble with another K2P subtype to operate, might not be targeted correctly to the plasma membrane in experimental cells, might require an unidentified accessory or regulatory subunit to reach the surface, or might have a predominantly intracellular location. However, our speculations were suspended by the discovery that a single lysine residue (K274) was crucial to K2P1 function [19••] (Figure 2).

K2P1 springs to life in both *Xenopus laevis* oocytes and tissue culture cells if K274 is mutated. Unexpectedly, K2P1 activity is observed on all tested changes to the site. K2P1 is active when the charge at the site is maintained (K274 to arginine) or reversed (K274 to glutamine), or when the residue is larger (K274 to tyrosine) or smaller (K274 to cysteine). Lysine was found to be unique at the site because it is the only residue subject to covalent modification by a protein conserved from yeast to mammals, the small ubiquitin-related modifier protein SUMO. Associated previously with nuclear import and/or export, activity and half-life of transcription factors [20–22], the SUMO pathway is now observed to function in its entirety at the plasma membrane [19••].

Thus [19••], yeast two-hybrid analysis, immunohistology and biochemical studies show K2P1 channels to interact with SUMO conjugating enzyme (Ubc-9 ligase) at the plasma membrane. K2P1 is modified by SUMO only at position 274 and the peptide adduct is removed by SENP1, the SUMO specific protease. Biophysical studies reveal that K2P1 is silent when it bears the adduct and active when SUMO is absent. The effect is reversible so that sumoylation and desumoylation can be observed to silence and awaken single K2P1 channels in plasma membrane patches (Figure 2). Finally, the phenotype of active K2P1 is revealed: a 32 pS, classical open rectifier. Moreover, K2P1 shares a conserved 1st P loop histidine that mediates potassium-dependent sensitivity to external pH via protonation, as seen with K2P3 and K2P9 (more below). Other membrane proteins also appear to be sumoylated [19••], suggesting that the pathway operates more broadly.

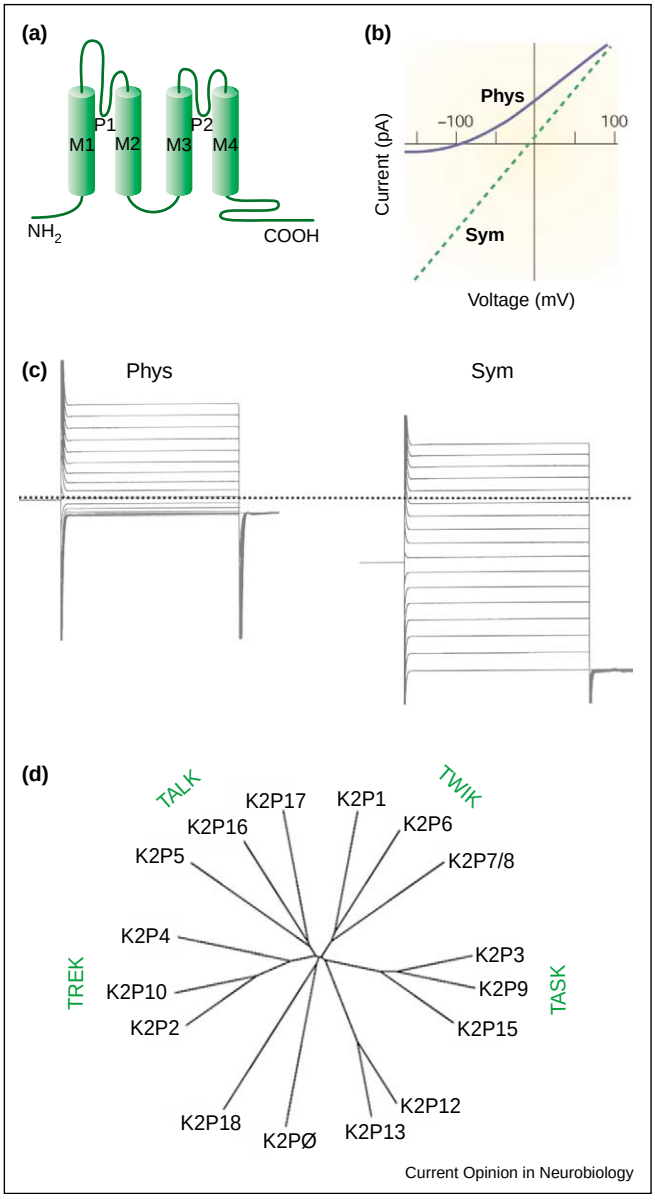
Efforts to correlate K2P1 activity with native currents are now emboldened! Abundant K2P1 transcripts in cerebellar granule neurons (CGN) have suggested a role for the channel in the standing outward potassium leak current I_{Kso} [9]. Indeed, characterization of I_{Kso} ascribed roles for four distinct components with attributes similar to those of K2P3, K2P9, K2P10 and a Type 4 channel — so named because it was distinct from any known K2P channel [23]. The biophysical signature of Type 4 channels described by Han *et al.* [23] is now seen to be a good match for many of the features of active (desumoylated) K2P1 channels [19••].

A protein partner that advances the TASKs

K2P3 (known also as TASK1, OAT1 and TBAK1) is expressed throughout the CNS. The channel appears to be a component of I_{KSO} currents in CGNs [23,24], to be a target for volatile anesthetics (which increase channel activity) [25] and to be involved in oxygen sensing in the brain and carotid body [26,27]. The channel is expressed in the heart, where it appears to be part of the cardiac action plateau current I_{Kp} [28,29], and in taste buds [30]. Acidosis-induced suppression of K2P3 in sensory neurons leading to depolarization and increased excitability has been implicated in the generation of neuropathic pain [31].

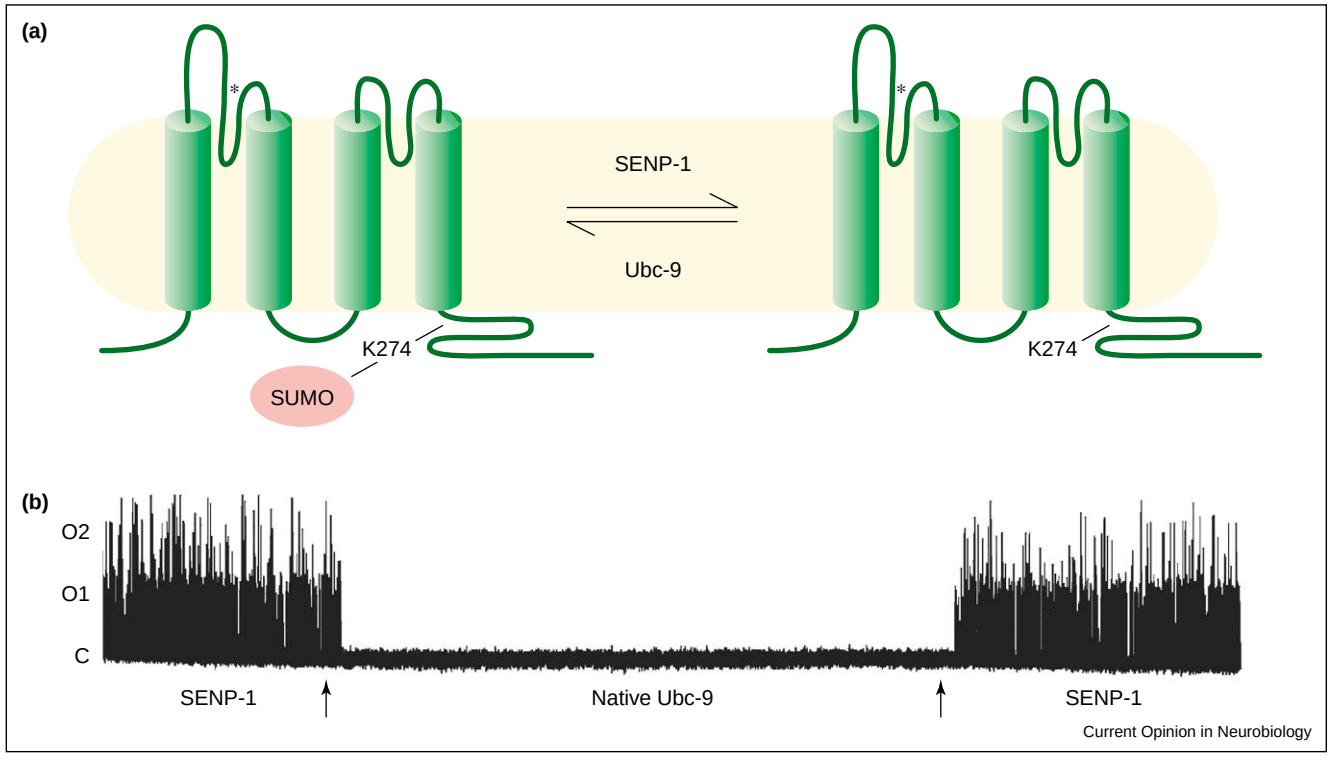
K2P3 [28,29,32] and K2P9 (TASK3) [33] are notable for their homology and shared sensitivity to external pH. This feature is conferred by a histidine in the 1st P loop that is protonated upon extracellular acidification, leading to channel inhibition (Figure 3). Titration of two histidine

Figure 1



The K2P channels are potassium-selective background leaks. K2P channels control membrane potential by passing potassium ions across the physiological voltage range, thereby influencing how excitable cells, such as neurons, respond to electrical inputs and propagate electrical information to adjacent cells. The nature of leak and membrane potential are considered further elsewhere [4]. **(a)** K2P subunits have a unique body plan with 2 pore forming P loops and 4 transmembrane domains (M1–M4). Two subunits come together to form a potassium selective pore. The 2 P loop proteins in *S. cerevisiae* and *C. elegans* have eight and four transmembrane domains, respectively. **(b)** K2P channels (in this case, K2PØ [3]) show Goldman-Hodgkin-Katz (open) rectification, passing larger outward than inward currents under physiological conditions (Phys) of high internal and low external potassium levels; the channels pass currents that change in a linear fashion with membrane potential when potassium levels are symmetrical (Sym). **(c)** Raw current traces from K2PØ studied by two-electrode voltage clamp demonstrating attributes expected for an open potassium-selective pore [3]; currents rise instantly with voltage steps (at the single channel level this is due to channels that are open before the step) and show open rectification as described in (b). Dashed line is 0 mV, Phys and Sym indicate 5 mM and 140 mM bath potassium, respectively. **(d)** As identification of K2P channels proceeds, structurally and functionally distinct subgroups are emerging that have names of historic origin: TWIKs: first described as a weak inward rectifier, K2P1 is now recognized to be a classical open rectifier similar to K2PØ that has been awakened by desumoylation (more below) [19••]. TASKs: K2P3 and K2P9 are acid-sensitive channels inhibited by protonation of a histidine in the first P domain when the pH of the bath solution is lowered. TREKs: K2P2 that was named TWIK-related in an early report. TALKs: K2P16 and K2P17 show more activity when the external solution becomes alkaline (see glossary).

Figure 2



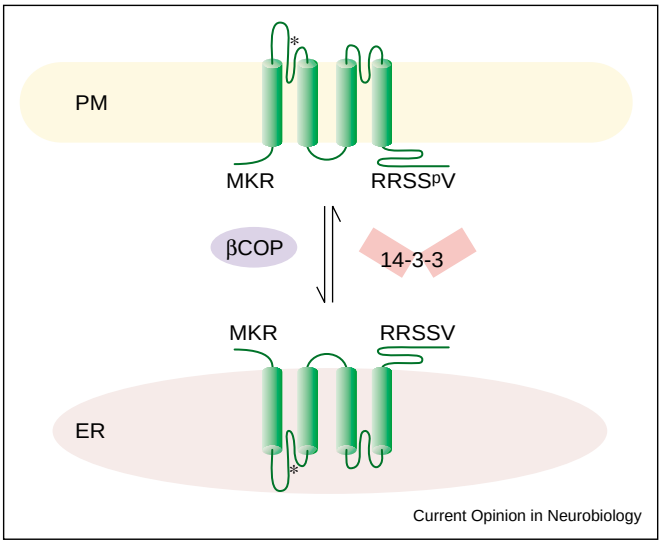
Reversible, covalent modification by SUMO regulates K2P1 activity. K2P1 has been electrically silent at the plasma membrane in experimental cells [15,16] because of linkage of SUMO by native SUMO ligase [19••]; desumoylation has opened the door for its biophysical characterization [19••]. Why clones of K2P7/8, K2P12 and K2P15 are silent at the membrane remains to be revealed. **(a)** Native SUMO conjugation machinery is active at the plasma membrane and silences K2P1. The covalent linkage of SUMO protein to the lysine at position 274 in K2P1 (K274) requires the E2 conjugating enzyme Ubc-9 and can be reversed by the desumoylating protease SENP-1. **(b)** Reversible SUMO modification of K2P1 and its association with activity and silence of the channels can be seen with patches excised from *Xenopus* oocytes. A 4 min continuous record shows an inside-out patch with active K2P1 channels excised from a cell expressing K2P1 and the SUMO protease SENP-1. When the patch is inserted into a naïve cell, the inner surfaces of the channels are exposed to native Ubc-9 and the channels are silenced. Channels return to full activity when the patch is withdrawn and inserted into a cell overexpressing only SENP-1. Arrows indicate insertion of patch into each new cell. The asterisk denotes the position of histidine 122 that confers sensitivity to lowered external pH.

residues in the K2P3 pore proceeds in a potassium-sensitive fashion with suppression of half the current at pH 7.26 in 5 mM potassium [12,29]. At baseline in experimental and native cells, K2P3 channels manifest a small conductance (~10 pS), brief openings (<1 ms) and low open probability (~0.05). Thus, small changes in pH have a significant influence on the already low basal activity of K2P3.

Yeast two-hybrid analyses and biochemical studies with K2P3 [34] and K2P9 [35] reveal that these members of the family are born to the plasma membrane out of conflict between two opposing trafficking motifs on the channel and competition for the sites by native intracellular binding partners (Figure 3). Dibasic sites on the channel interact with coatamer proteins (β-COP; see glossary) to hold K2P3 in the endoplasmic reticulum (ER). Escape from the ER is regulated by phosphorylation of a single site on the K2P3 C-terminus. The phosphorylated channel binds 14-3-3β, a soluble dimeric adaptor protein found in all mammalian cells [34,35]; this suppresses β-COP binding enabling forward trafficking of the channel to the surface [34]. This mechanism is shared not only by K2P3 and K2P9 but appears to modulate trafficking of other membrane proteins, such as nicotinic acetylcholine receptors and major histocompatibility antigen class II-associated invariant chains [34]. A role for 14-3-3 in correct assembly of multimeric protein complexes and masking of retention motifs has since been shown to permit escape of other membrane proteins from the ER [36]. The influence of p11, an annexin II subunit, in K2P3 forward trafficking has been proposed [37], although limited tissue distribution of p11 protein suggests a role in fine-tuning expression levels or locale.

In reverse fashion, K2P1 in renal proximal tubule appears to have a partner that promotes retrograde trafficking away from the surface [38]. EFA6 is an exchange factor involved with membrane protein recycling and actin

Figure 3



K2P3 and K2P9 are released to the plasma membrane (PM) by 14-3-3 binding. K2P3 and K2P9 are retained and recycled to the endoplasmic reticulum (ER) as a result of binding β-COP to dibasic motifs. Phosphorylation of a C-terminal release site enables 14-3-3 binding, suppresses β-COP association and enables forward trafficking of correctly assembled channels to the plasma membrane (PM) [34,35]. The asterisk denotes histidine in the 1st P loop that confers sensitivity to low external pH [12,29,33].

organization. In Mabin-Darby canine epithelial kidney cells, K2P1 interacts with EFA6 in an ADP ribosylation factor 6-dependent manner to favor trafficking from the plasma membrane to recycling endosomes.

Protein kinases can be a real turn-off

K2P2 channels (known also as TREK-1 and hTPKC-1) are widely expressed, showing notable abundance in hippocampus; currents increase on exposure to arachidonic acid, mechanical stretch and volatile anesthetics, and decrease flux with lowered temperature via a protein kinase A (PKA)-dependent pathway [16,39–42]. Exploring effects of PKA on K2P2, phosphorylation was found to produce something more novel than simply lower open probability (that is, less leak). Single K2P2 channels reversibly inter-convert between leak and voltage-dependent phenotype [43]. Thus, K2P2 is an open rectifier when the PKA site (serine 348) bears no phosphate or is mutated to alanine, passing large currents both inward and outward in symmetrical conditions (Figure 4a), and larger outward currents under physiological conditions. Conversely, phosphorylated channels, and those altered to aspartate at the site, pass more outward current even in symmetrical potassium because of voltage-dependent changes in open probability (showing a half-maximal activation voltage positive to 0 mV that does not change with E_K — unlike the 2P–8TM outward rectifiers TOK1 and KCO1 [5,44]). This phenotypic alchemy should enhance excitability because less potassium leak simply enables depolarization to reach the firing threshold, whereas activation at supra-threshold potentials facilitates recovery and repetitive re-firing.

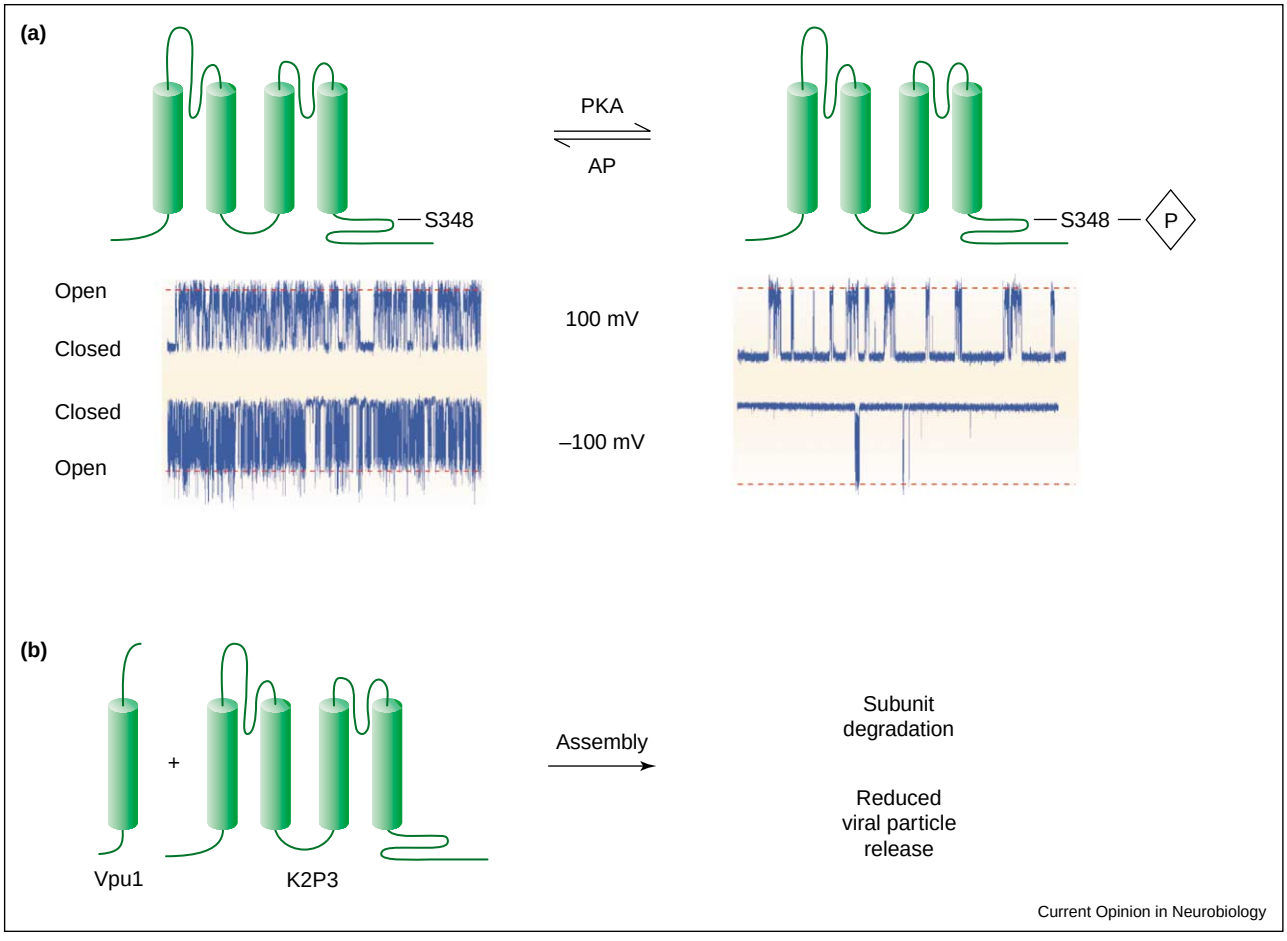
A foreign partner

Recently, K2P3 was revealed to interact with Vpu-1, an HIV-1 encoded membrane protein that enhances the release of progeny virions from infected cells [45••]. Vpu-1 is an 86 residue, single membrane-spanning peptide with homology to the first transmembrane domain of K2P3 (raising the intriguing idea that the molecule might have evolved through molecular piracy). Vpu-1 and K2P3 physically interact in lymphoid tissues in patients with AIDS to diminish K2P3 currents. In primary CD4+ T cells infected with HIV-1, this interaction results in degradation of the channel (Figure 4b); reciprocally, overexpression of the channel appears to have detrimental effects on the pathogen, leading to degradation of Vpu-1 protein and release of fewer viral particles. Vpu-1 acts similarly to the native single transmembrane partners of voltage-gated potassium channels called MinK-related peptides (MiRPs) — MiRPs assemble co-translationally with P loop proteins to modify trafficking and turnover (in addition to voltage-dependent gating, fine ionic discrimination and pharmacology of the pores) [46]. Similarly, overexpressing a voltage-gated potassium channel fragment with just the first of six transmembrane domains in mouse heart leads to trapping of intact channels in ER, current suppression and cardiac arrhythmia [47].

Other emerging roles for K2P channels in health and disease

The firing of CGNs is subject to tonic inhibition due to suppression of excitability by persistent γ-aminobutyric acid (GABA)-mediated chloride conductance. In CGNs of mice in which the gene for the α_6 subunit of the $GABA_A$

Figure 4



PKA-mediated downregulation and assembly-dependent degradation. **(a)** K2P2 is an open rectifier when the PKA site (serine 348) bears no phosphate, and passes inward and outward currents in symmetrical potassium conditions [43]. When the PKA site is phosphorylated, the open probability of the channel decreases and cloned (in addition to native hippocampal) K2P2 channels reversibly convert from the open rectifier to the voltage-dependent phenotype. **(b)** Vpu-1 is a HIV encoded protein that enhances the release of progeny virions from infected cells [45••]. Vpu-1 has a single transmembrane domain that is highly homologous to the first transmembrane segment of K2P3. Vpu-1 and K2P3 physically interact in lymphoid tissues in patients with AIDS, promoting channel degradation and diminished K2P3 currents. Reciprocally, channel overexpression leads to degradation of Vpu-1 protein and decreases the number of viral particles that are released. Abbreviations: AP alkaline phosphatase; PKA, protein kinase A.

receptor is disrupted, K2P3 conductance is upregulated, an adaptive response that maintains normal electrical behavior [48] (and is likely to promote cell survival because inappropriate neuronal activity can trigger cell death pathways [49]). CGNs receive multiple excitatory stimuli and act as filters to integrate dynamically the signals into firing patterns transmitted to Purkinje cells, and tonic inhibition is a key determinant of both quantal integration and excitatory output [50]; it has plausibly been suggested that K2P3 channel activity fine-tunes responsiveness when GABA receptors are normally expressed.

Representational difference analysis has identified amplified expression of K2P9 transcripts in human carcinomas of breast, lung, colon and prostate, with overexpression as high as 100-fold in 44% of breast tumors [51•]. The association might be etiological — mutation of K2P9 to abolish ion conduction pore function abrogates oncogenic potential in a model system [52]. The suggested oncogenic mechanism is loss of resistance to apoptosis, an important mechanism to prevent inappropriate cell division, raising the idea that K2P9 inhibitors might prove therapeutic. Previously, transcripts for the voltage-gated potassium channel HERG were found at increased levels in several distinct human tumors [53], and overexpression of its murine isoform associated with an aggressive phenotype transferable to immuno-deficient mice on implantation of transfected cells [54].

Conclusions

Potassium ions leak via dedicated, highly regulated pathways: the K2P channels. The K2P channels reveal an

impressive diversity of mechanisms to control signaling of excitable cells dynamically, and two core principles can be enunciated [4]. First, K2P regulation alters one of three attributes subject to change in any ion channel: channel number at the site of operation, open probability or unitary conductance. Here, we have focused on protein partners that modulate K2P channels (and also appear to act on other membrane proteins). Thus, SUMO controls open probability by reversible linkage to K2P1; 14-3-3 regulates channel number by controlling the forward transport of K2P3 and K2P9 to the plasma membrane; PKA-mediated phosphorylation decreases the open probability (and more!) of K2P2; and, Vpu1 diminishes channel number by increasing the degradation of K2P3. Second, low basal activity of K2P channels enables rapid and significant change in flux. In the case of cloned K2P1, sumoylation speedily shifts channels from silent to active. Such all-or-none behavior is seen *in vivo*, for example, in bag cell neurons of *Aplysia* in which a covert class of calcium channel emerges on activation of protein kinase C [55] by an as yet undetermined mechanism. Similarly, rapid dephosphorylation increases activity of cloned and native K2P2 [43]. Another recently reported mechanism to alter channel number rapidly is hormone-induced delivery of channels by vesicles resident just below the plasma membrane [56].

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- • of special interest
- •• of outstanding interest

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